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Skin Cancer (T Ito, Section Editor)

Diagnosis and Management of Acral Lentiginous Melanoma

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Opinion statement

Melanoma is one of the most aggressive malignant skin tumors and its incidence has been increasing worldwide in recent decades. Among the four subtypes, acral lentiginous melanoma (ALM) shows the highest incidence in Asian countries, whereas ALM comprises only 1% of all melanomas in white populations. Early clinical diagnosis of ALM is essential, but early ALM lesions are often difficult to diagnose because the pigmentation of the lesions sometimes follows the skin marking of the palms and soles, resulting in an asymmetrical appearance and an irregular border in both ALM and benign melanocytic nevus. To overcome this difficulty, dermoscopy was introduced, and determination of the patterns by this method is essential for accurate clinical diagnosis of ALM. Although recent clinical trials have demonstrated that immune checkpoint inhibitors and BRAF/MEK inhibitors showed significantly improved overall survival of patients with advanced melanoma, ALM may be less susceptible to immune checkpoint inhibitors because of the poor immune response to the tumor. Therefore, strategies for enhancing the immune response to the tumor cells may be required when we apply immune checkpoint inhibitors in advanced ALM. In this context, imiquimod, dacarbazine, or interferon are possible therapies that may enhance the effectiveness of the immune checkpoint inhibitors. In addition to being known to have poor immunogenicity, ALM is also known to have infrequent *BRAF* mutation. Therefore, the majority of ALM patients may not benefit from therapy with BRAF/MEK inhibitors. However, some ALMs have mutations such as *KIT* and *NRAS* mutations, and therefore, targeted therapies may improve the survival of ALM patients in the future.

Introduction

Malignant melanoma carries a poor prognosis and its incidence has increased in recent decades [1]. Based on the clinical and histologic findings, malignant melanoma is classified into four subtypes: lentigo maligna melanoma (LMM), superficial spreading melanoma (SSM), acral lentiginous melanoma (ALM), and nodular melanoma (NM). ALM is rare in white populations, but has a higher incidence in Asian populations. According to previous reports, ALM accounts for 1 to 7% of all malignant melanomas in White populations, but for more than 50% in Asian populations [2–4]. A recent retrospective study demonstrated no significant difference in melanoma-specific survival or disease-free survival between ALM and non-ALM patients [5]. However, in future studies, ALM patients may show shorter survival because ALM has been reported to show poor response to immune checkpoint inhibitors and infrequent *BRAF* mutation. In this review, we discuss the diagnosis and management of ALM.

Diagnosis

Clinical appearance

ALM frequently develops on the hairless skin of the hand and foot. The plantar region has been reported to be the most common site of ALM [6], which also commonly occurs in the subungual area, especially the great toe followed by the thumb [6]. In the non-subungual area, ALM initially appears as an atypical pigmented macule. Along with the progression, the lesion extends with irregular borders. With the evolution of vertical growth, an elevated plaque or nodule develops within the pigmented macule, and the lesion is sometimes associated with ulceration. In cases with subungual ALM, the nail and nail bed may show a longitudinal uneven pigmented band with an irregular border. The pigmentation sometimes extends to the nail fold, which is called the Hutchinson sign, and it may also spread to the digital skin. Along with the progression, splitting or destruction of the nail plate may develop. For the screening of ALM, the clinical criteria known as the ABCDE rule (lesions with asymmetry, border irregularity, color variation, diameter greater than 6 mm, and evolving size, shape, or color) are used as with other types of malignant melanoma. However, even with such criteria, it is not always easy to differentiate early malignant melanoma from benign melanocytic nevus [1]. Especially when located in the acral region, the pigmentation follows the skin marking of the palms and soles, resulting in an asymmetrical appearance and an irregular border even in cases with melanocytic nevus. To increase the sensitivity, the use of dermoscopy has been shown to be a useful tool for the diagnosis of ALM [7].

Dermoscopy

Dermoscopy significantly improved the clinical diagnosis of ALM. Some previous studies suggested that the dermoscopic findings may be more critical than the histologic findings in the early phase of ALM [8, 9]. A parallel ridge pattern (PRP), which can be easily observed as pigmentation parallel with the ridges of the skin, is the most important finding of ALM in dermoscopy. Saida et al. reported that the sensitivity and specificity of PRP for ALM were 86.4 and 99%, respectively [10]. In contrast, a parallel-furrow pattern (pigmentation following the furrows), lattice-like pattern (linear pigmentation following and crossing the furrows), or fibrillar pattern (filamentous pattern with parallel fine streaks

crossing the dermatoglyphics in a slanted direction) is frequently observed in melanocytic nevus. Such benign features can also be seen in ALM but are usually found in association with PRP [7, 8, 10]. The detection of early subungual ALM is one of the most difficult parts of the clinical diagnosis. Dermoscopy has also been reported to be useful for the diagnosis of subungual ALM [7]. Most lesions with subungual ALM reveal a brown background with longitudinal irregular lines. In addition, it has been reported that a triangular shape of the band, which develops owing to an enlargement of the proximal edge of the longitudinal melanonychia, is a specific finding for subungual melanoma [7].

Histologic diagnosis

The histologic feature of ALM is broad lentiginous growth of melanoma cells [6, 11]. In cases with early lesions, the majority of the tumor cells present as single units that later coalesce into nests. Although this predominance of nests is an indicator of melanocytic nevus, melanocytic nevus can also show a proliferation as single cells, meaning that it is not a specific marker to distinguish between melanoma and melanocytic nevus. However, in melanocytic nevus, the tumor nests are usually vertically oriented, whereas the nests of ALM are often located parallel to the epidermis. In addition, the nests of melanocytic nevus are cohesive, similar in size, and well circumscribed, whereas the nests of ALM are usually noncohesive, variously sized, and poorly circumscribed [6, 12].

Most of the tumor cells in ALM are located near the dermal-epidermal junction, especially at the periphery of the lesion, but some of the tumor cells can be observed in the upper layers of the epidermis along with progression. However, these findings can also be observed in melanocytic nevus. But in melanocytic nevus, the tumor cells tend to ascend along the furrow, whereas in ALM, they tend to ascend along the ridge, which is consistent with the dermoscopic findings [12, 13]. Therefore, making perpendicular sections to the ridges and furrows is essential to differentiate between ALM and melanocytic nevus.

The size of the nuclei is also helpful to distinguish ALM from melanocytic nevus [13]. The nuclei of melanocytic nevus are usually smaller than those of the adjacent keratinocytes. Thus, when the nuclei of the tumor cells are larger than those of the keratinocytes, the possibility of ALM should be considered. As for the shape of the nuclei, the nuclei of melanocytic nevus are usually oval and sometimes show horizontal arrangement. In contrast, a horizontal arrangement of nuclei implies ALM. Some authors have suggested that thick dendrites or long dendrites reaching the upper parts of the epidermis support a diagnosis of malignancy, and HMB45 immunostaining is useful to assess the dendrite shape [13].

Histologic diagnosis of early subungual ALM is often challenging. One of the important features of early subungual ALM is the increased number of melanocytes. ALM usually shows > 30 tumor cells in 1-mm width of epidermis, while benign melanocytic nevus rarely presents such a finding [13]. However, it should be taken into consideration that some subungual ALM may show low cellularity similar to that of melanocytic nevus. Cellular atypia and ascent are other supportive findings for non-subungual ALM, but in most cases with early subungual ALM, the tumor cells may not show cellular atypia or ascent.

In conclusion, the histologic features of ALM are often subtle, whereas plantar melanocytic nevus may show ascent or nuclear atypia, which are known to be signs of malignancy [13]. Therefore, clinical information including the dermoscopic findings is sometimes essential for the diagnosis of ALM.

Management

Surgery

As with other types of melanoma, the standard therapy for primary ALM is wide local excision. The vertical level of the excision depends on the thickness of the tumor. As for the horizontal margins, wide local excision with 3- to 5-cm margins was previously recommended for the treatment of invasive melanoma [14, 15]. However, several studies have demonstrated no significant difference in overall survival or local recurrence rate between patients treated with narrow-margin excision and those treated with wide-margin excision. Balch et al. evaluated 2- versus 4-cm margins for melanoma of 1 to 4 mm in thickness and showed no significant difference in overall survival or local recurrence [16]. In addition, Khayat et al. evaluated 2- versus 5-cm margins for melanoma of ≤ 2 mm in thickness in a randomized study and demonstrated no significant difference in the rate of recurrence or the 10-year overall survival rate [15]. Moreover, McKinnon et al. demonstrated that if the surgical margin was ≥ 1 cm, it was no longer associated with the local recurrence rate in melanoma of ≤ 2 mm in thickness [17]. From these results, the current AJCC Guidelines recommend 1-, 1- to 2-, and 2-cm margins for invasive melanoma of ≤ 1, 1.01 to 2, and > 2 mm in thickness, respectively [18]. A recent retrospective study focused only on ALM revealed that local recurrence was also independent of whether the excision margin was 1 cm or more in thin ALM (thickness ≤ 1 mm), whereas multivariate analyses revealed that 2-cm margins were associated with a reduced rate of local recurrence when compared with < 2-cm margins in thick ALM (thickness > 1 mm) [19].

As for melanoma in situ, Bartoli et al. reported that in cases with smaller lesions of less than 2 cm diameter, there was no significant difference in local recurrence between 3-mm margins and wider margins [20]. On the other hand, Kunishige et al. showed 5-mm margins for excision of melanoma in situ to be inadequate, clearing only 86% of tumors, and they recommended 9-mm margins for standard excision [21]. Therefore, a current guideline recommends 5- to 10-mm margins for melanoma in situ [18].

After surgical excision, primary closure, skin grafting, secondary intention healing, and local and free flaps are performed with careful assessment of the functional and cosmetic aspects. Primary closure is the simplest and presents the fewest complications. However, as ALM frequently develops on the sole of the foot, primary closure can seldom be performed because of lack of mobility of the skin in that area. A full-thickness skin graft is often used for the reconstruction when primary closure is impossible, and recent reports have shown the usefulness of negative pressure closure (NPC) for the stabilization of skin grafts [22]. Several reports have suggested that the functional and cosmetic outcomes of secondary intention healing were better than those of skin grafts, although secondary intention healing requires a longer treatment period [23]. NPC has also been reported to be useful for improving the functional and cosmetic outcomes as well as for preventing infections during secondary

intention healing after wide excision of foot ALM [24]. Local flaps such as a medial plantar flap and a distally based sural flap may be used for a large skin defect after wide excision of heel ALM and show great results in terms of the functional and cosmetic aspects. However, these flaps may damage the lymph flow to the regional lymph nodes. Our previous study using a mouse model demonstrated that damage to the lymph flow to the regional lymph nodes promoted tumor progression via impaired immune response to the tumor [25]. Therefore, we suggest that such flaps are not recommended for reconstruction of skin defects after wide excision of high-risk ALM for recurrence.

In cases with subungual ALM, surgical excision is always challenging because of the close distance between the nail and the underlying bone. Wide excision with phalanx amputation may be considered for the treatment of thick subungual ALM. However, the amputation would result in substantial morbidity and deformity, and no previous reports have shown improvement of the disease-free survival or overall survival of subungual ALM as a result of amputation. Conservative surgery with excision at the level of the distal phalanx could be sufficient for removing the tumor cells in situ. In addition, such surgery may also achieve complete excision of minimally invasive subungual ALM. Indeed, there have been numerous reported cases of patients who did not show recurrence after receiving such surgery [26]. Skin grafting after total nail unit excision provides much better cosmetic and functional outcomes than does amputation. Therefore, conservative surgery without amputation should be considered for subungual ALM with early lesions, although further analyses of prospective studies with large numbers of patients are required for evaluating the validity of such surgery. In this context, a clinical trial of nonamputative preservation surgery for subungual melanoma (JCOG1602, J-NAIL) is currently ongoing in Japan.

Sentinel lymph node biopsy and elective lymph node dissection

Sentinel lymph nodes (SLNs) are the first nodes in the lymphatic basin from the primary tumor drains. The presence or absence of melanoma cells in an SLN is well known to be an independent factor for the prognosis, and therefore, SLN biopsy is now recommended in melanoma patients with intermediate-thickness tumors [27]. Several reports demonstrated that ALM patients with positive SLNs had significantly shorter disease-free survival and overall survival [28]. In addition, a recent study revealed that in thin melanoma, among all the histologic types, ALM showed the highest frequency of positive SLNs and that ALM was an independent factor of SLN positivity [29]. Currently, ELND is recommended when the SLN biopsy results are positive for metastasis [27]. However, a recent randomized trial (MSLT-II), which compared between positive SLN patients with immediate ELND and those without it, revealed that immediate ELND did not improve disease-specific survival [30••]. In addition, our study suggested that ELND may rather promote tumor growth via an impaired adaptive immune response [25]. Therefore, the current recommendation for immediate ELND after positive SLN biopsy may change in the near future.

Molecularly targeted therapy

Mutation of the serine-threonine kinase *BRAF* gene is the most frequently observed mutation in malignant melanoma, occurring in 40 to 60% of all cases [31]. Such mutation activates B-raf protein, resulting in activation of the mitogen-activated protein kinase (MAPK) pathway, which includes Raf, MEK, and ERK. Then, activated ERK phosphorylates a downstream transcriptional factor, leading to increased proliferation and survival of the tumor cells [32]. The majority of patients with mutations have valine replaced with glutamine in the 600 codon (V600E) and less frequently with lysine (V600K) or arginine (V600R). In a randomized phase 3 study (BRIM-3) using vemurafenib, a BRAF inhibitor, a statistically better response ratio was achieved with prolonged progression-free and overall survival than with dacarbazine (DTIC) [33]. Another BRAF inhibitor, dabrafenib, also showed similar results to those of the BRIM-3 study (BREAK-3) [34]. The MEK inhibitor, which inhibits downstream BRAF, showed prolonged progression-free and overall survival when compared with DTIC in patients with *BRAF*-mutant advanced melanoma [35]. Because MEK activation has been identified as an important drug-resistant mechanism of the BRAF inhibitor in BRAF mutant melanoma, combined use of BRAF and MEK inhibitors was tested in a clinical trial. As a result, the phase 3 trial (COMBI-d) of dabrafenib and a MEK inhibitor (trametinib) showed an improved response rate and prolonged progression-free and overall survival when compared with dabrafenib alone [36•]. Not only did it achieve an improved response, but this combination also reduced the occurrence of squamous cell carcinoma, which is commonly seen in BRAF inhibitor monotherapy [37]. Therefore, combination therapy using BRAF and MEK inhibitors is now recommended for patients with advance melanoma with the *BRAF* mutation [38]. However, while *BRAF* mutations are common in melanoma in regions of high sunlight exposure, ALM shows much lower frequency of the *BRAF* mutation [39]. In previous reports, the frequency of *BRAF* mutations in ALM was only 15 to 20% [40–42], whereas in SSM, it was 50 to 65% [43, 44].

On the other hand, the *KIT* mutation and/or amplification are more commonly found in ALM than in other types of melanoma (10–20% [45, 46]). Several phase II trials have demonstrated promising results with KIT inhibitors for patients with *KIT* mutant melanoma [47]. Besides the *KIT* mutation, *NRAS* mutations are also detected in ALM. N-ras regulates the phosphoinositide 3-kinase (PI3K)/Akt cascade as well as B-raf activation, resulting in subsequent activation of the MAPK pathway. A recent clinical trial with MEK162, a potent MEK inhibitor, has shown some activity in patients with *NRAS* mutant melanoma [48, 49]. Therefore, despite the low frequency of the BRAF mutation in ALM, a certain percentage of ALM patients may benefit from novel therapies targeted to these molecules in the future.

Immune checkpoint inhibitors

PD-1 (programmed cell death-1) is a member of the immunoglobulin superfamily of proteins and is expressed mainly on the surface of T cells. PD-1 binds to two ligands, PD-L1 and PD-L2, and strongly inhibits TCR signaling and CD28-costimulation [50] [51]. CTLA-4 (cytotoxic T lymphocyte antigen-4) is also a member of the immunoglobulin superfamily and is normally expressed on the surface of conventional and regulatory T cells. CTLA-4 can compete with

CD28 for B7, turning off T cell receptor signaling [52]. Therefore, PD-1 and CTLA-4 are critical molecules that downregulate T cell activation. The recent development of immune checkpoint inhibitors against these molecules has led to great improvement in the treatment of advanced melanoma. Recent randomized clinical trials revealed that both anti-PD-1 and anti-CTLA-4 monoclonal antibodies have significantly prolonged the survival of advanced melanoma patients [53–55]. Currently, for patients with *BRAF* wild-type advanced melanoma, immune checkpoint inhibitors are recommended as the first-line therapy [38]. However, these previous studies comprised mainly white populations, in whom SSM and LMM are the major clinical types of melanoma. On the other hand, ALM has been reported to be less susceptible to immune checkpoint inhibitors than is SSM or LMM [56]. Similarly to the rates reported by the previous study, the best overall response rates of ALM and SSM treated with anti-PD-1 antibodies at our institute were 25% (3/12) and 80% (8/10), respectively (unpublished data). The number of tumor-infiltrating lymphocytes (TILs) has been shown to correlate with better response to immunotherapies [57]; however, the number of TILs in ALM was significantly lower than that in non-ALM [57]. Therefore, to recruit TILs, combination therapies consisting of immune checkpoint inhibitors with possible immune simulants should be evaluated to enhance the response of ALM to immune checkpoint blockade therapy. In this context, we would like to focus on the therapy that may elicit the immune response: imiquimod, chemotherapy, and/or interferons (IFNs).

Imiquimod

Imiquimod is a ligand of toll-like receptor 7 and stimulates immune cells including plasmacytoid dendritic cells to produce proinflammatory cytokines involved in the activation of immune cells and a shift toward the Th1 immune response [58]. A previous retrospective study demonstrated that 50 of 58 cases (86.2%) with lentigo maligna melanoma (LMM) showed clinical clearance, with a mean follow-up of 42.1 months and that imiquimod-induced inflammation was significantly associated with clinical or histologic clearance [59]. Topical imiquimod has also been shown to be effective for the treatment of LMM with positive surgical margins [60]. Although development of imiquimod-induced inflammation seems to be more difficult in the acral regions owing to the thick corneum and epidermis preventing absorption of the components, some reports have shown the effectiveness of imiquimod in both non-subungual and subungual ALM [58, 61]. Therefore, imiquimod may be a promising treatment for patients for whom surgery is not possible because of the patient's preference, comorbidities, or functional impairment. In addition, owing to its immunostimulatory effects, there have been some case reports of patients with in-transit metastases of melanoma successfully treated with anti-CTLA-4 antibody combined with topical imiquimod treatment [62, 63].

Chemotherapy

Chemotherapies have been used for cancer treatment owing to their cytotoxic effect against cancer cells. For patients with metastatic melanoma, chemotherapy with DTIC has served as the standard therapy for decades. However, responses to DTIC are known to be limited, and previous studies have never demonstrated a survival benefit with DTIC. Recent studies have clarified that

some of the chemotherapeutic drugs have immunomodulatory effects. In this context, Hervieu et al. demonstrated that DTIC has not only cytotoxic effects but also immunostimulatory effects [64]. They showed that DTIC elicits the expression of NKG2D ligands in melanoma cells, which directly promotes activation of NK cells and enhances tumor cell killing. In addition, the ligand recognition also promotes release by NK cells of IFN-γ, which upregulates major histocompatibility complex class I expression in the tumor cells and promotes the recognition by cytotoxic $CD8^+$ T lymphocytes [64]. This study provides the possible combination therapy of immune checkpoint inhibitors with DTIC to enhance the immunostimulatory effects for melanoma.

Interferons

Interferons (IFNs) are a group of naturally existing glycoproteins that are secreted by many kinds of cells, especially in response to viral infection. Type I IFNs (IFN-α and IFN-β) bind to IFN-α receptors 1 and 2. This binding promotes phosphorylation of JAK1 and TK2, followed by STAT1 and 2, and thereby induces translocation of ISGF3 (IFN-stimulated response elements) to the nucleus and its binding to the promoter of the type I IFN-responsive gene. Type I IFNs show numerous biologic activities such as immunoregulatory, antiangiogenic, differentiation-inducing, antiproliferative, and antiapoptotic activities [65]. As for the immunoregulatory effects, type I IFNs enhance the dendritic cell response to tumor antigens and promote antigen cross-presentation that leads to antitumor immunity [65, 66]. In addition, type I IFNs promote a shift from Th2 to Th1 polarization, resulted in enhancing cellular-mediated cytotoxicity [67, 68]. IFNs have been widely used as adjuvant therapy for patients who achieve removal of the primary tumor. Although the benefit of adjuvant IFN was small, previous randomized clinical trials have shown the effect of high-dose IFN-α or pegylated IFN-α as an adjuvant therapy [69]. However, recent randomized trials have shown that the BRAF inhibitor and immune checkpoint inhibitors showed significantly prolonged survival when used as adjuvant therapies [70, 71]. Therefore, the recommendation for adjuvant therapy for high-risk resected melanoma will shift to these new therapies. Moreover, because IFNs can enhance dendritic cell function and Th1 polarization, IFNs may provide synergistic effects when simultaneously used with immune checkpoint inhibitors. In this context, clinical trials of combined therapy of IFN-α with anti-CTLA-4 or anti PD-1 antibody for advanced melanoma are currently ongoing [69].

Summary

ALM is characterized by a long radial growth phase and is sometimes difficult to diagnose at the early stage of the disease. The recently developed dermoscopy technique has become a quite helpful tool for differentiating ALM from benign melanocytic nevus. The clinical course of ALM differs from those of SSM and LMM, which are common in white populations. The response rate of immune checkpoint inhibitors has been reported to be low for ALM. Moreover, the frequency of the *BRAF* mutation has been shown to be much lower in ALM, meaning that patients with ALM could not benefit from recently developed therapies. Therefore, further studies are required to establish novel therapies especially for ALM patients.

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Compliance with Ethical Standards

Conflict of Interest
Yoshiyuki Nakamura and Yasuhiro Fujisawa declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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